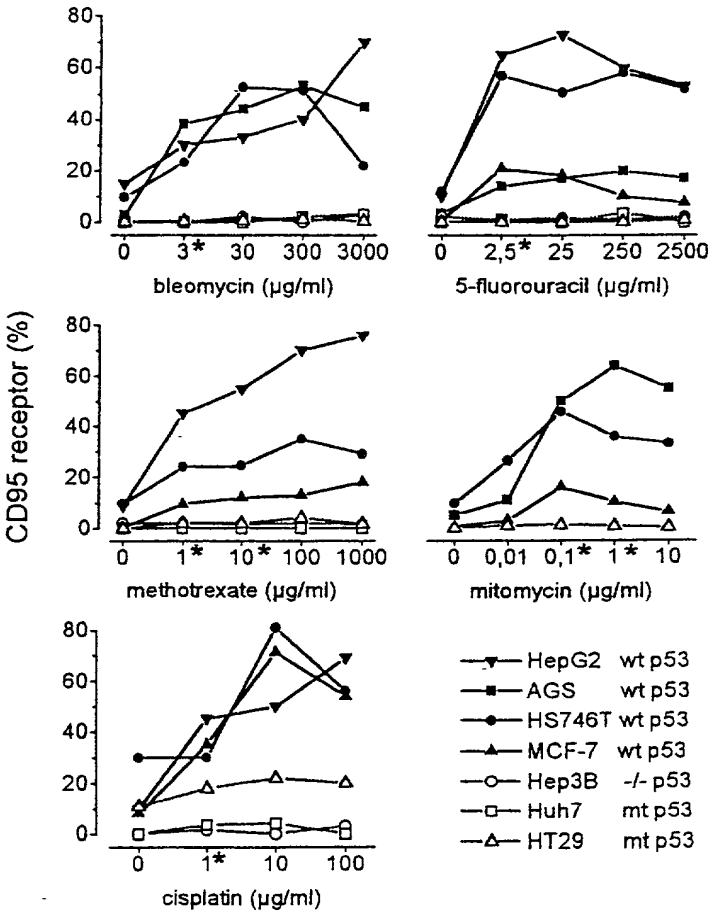
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bleomycin (µg/ml)
5-fluorouracil (µg/ml)
methotrexate (µg/ml)
mitomycin (µg/ml)
cisplatin (µg/ml)
HepG2 wt p53
AGS wt p53
HS746T wt p53
MCF-7 wt p53
Hep3B -/- p53
Huh7 mt p53
HT29 mt p53

Fig. 1

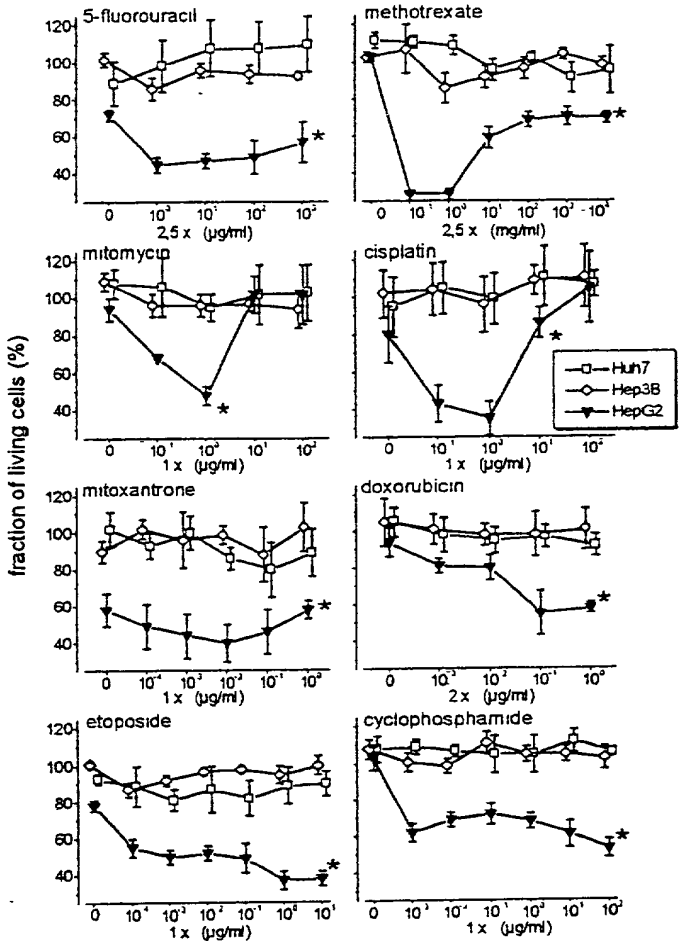
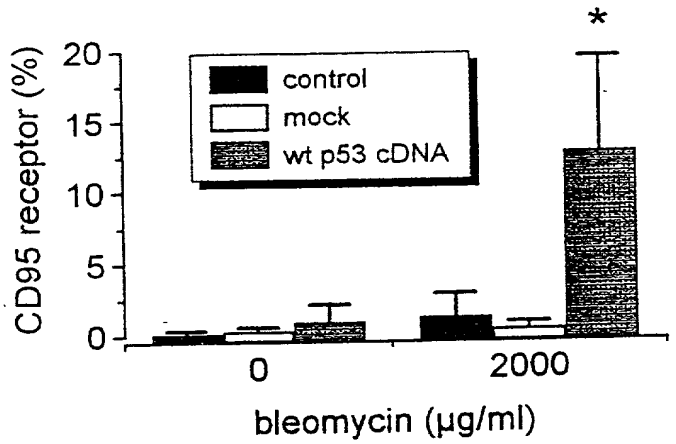

5-fluorouracil
methotrexate
mitomycin
cisplatin
mitoxantrone
doxorubicin
etoposide
cyclophosphamide
fraction of living cells (%)
Huh7
Hep3B
HepG2
2,5 x (µg/ml)
2,5 x (mg/ml)
1 x (µg/ml)
2 x (µg/ml)

Fig. 2


*
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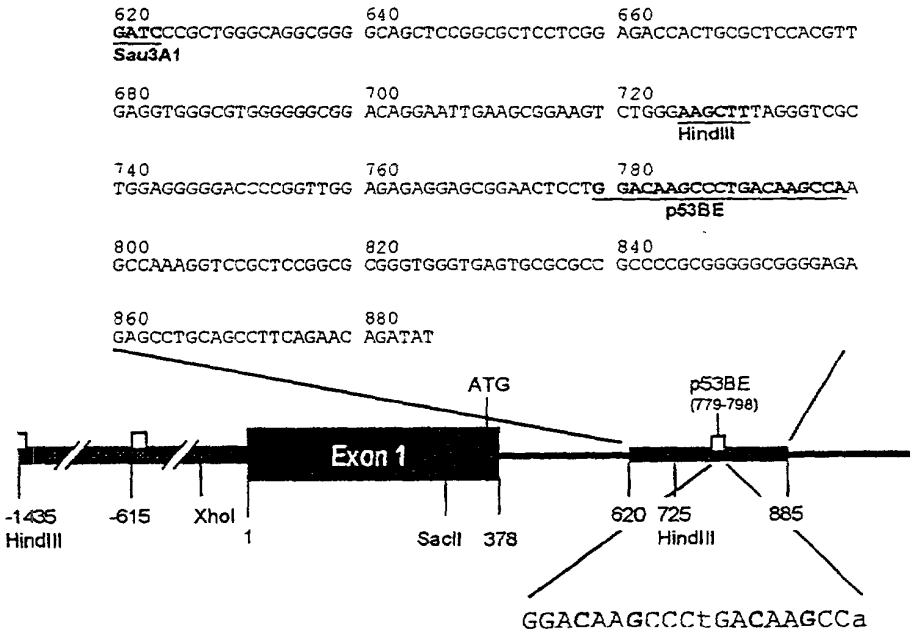
15
10
5
0
CD95 receptor (%)
control
mock
wt p53 cDNA
0
2000
bleomycin (µg/ml)

Fig. 3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720
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HindIII
740
TGGAGGGGGACCCCGGTTGG
760
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780
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p53BE
800
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860
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880
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ATG
p53BE
(779-798)
Exon 1
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XhoI
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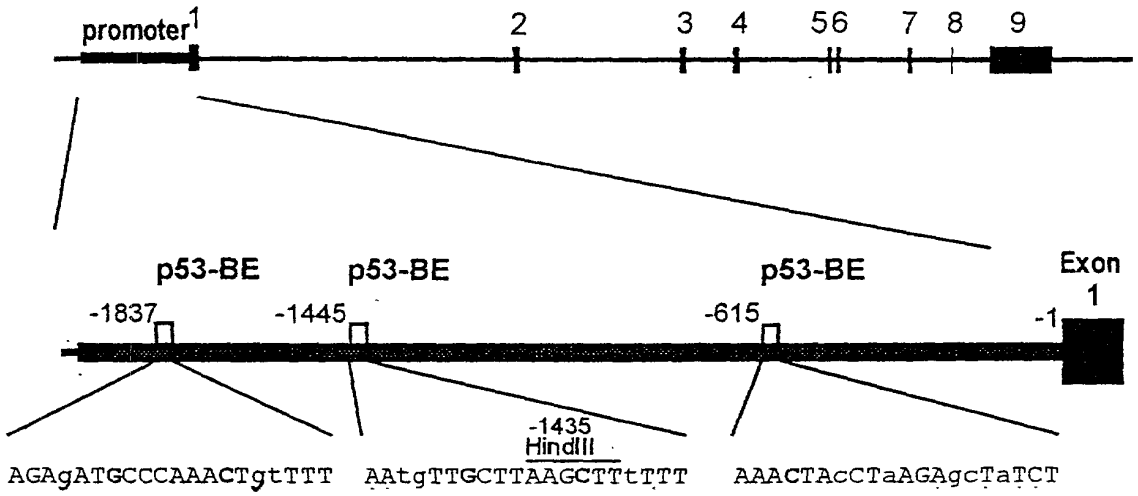
Fig. 4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7
8
9
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HindIII
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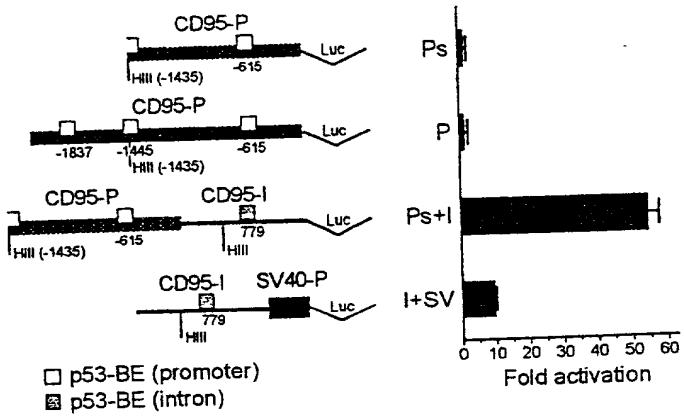
Fig. 5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HIII (-1435)
CD95-P
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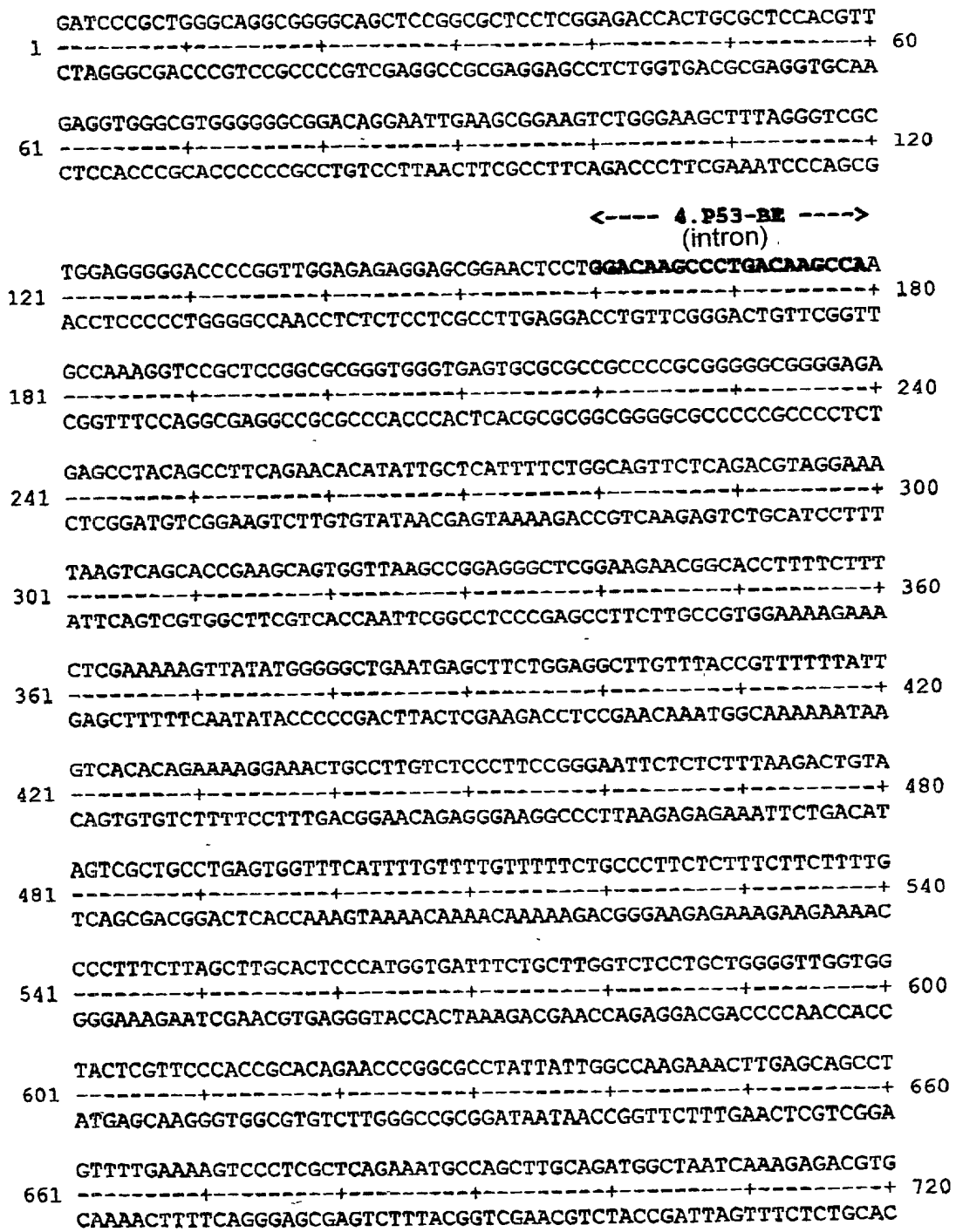
CD95-I
-615
779
HIII (-1435)
HIII
Luc
CD95-I
SV40-P
779
HIII
Luc
p53-BE (promoter)
p53-BE (intron)
Ps
P
Ps+I
I+SV
0 10 20 30 40 50 60
Fold activation

Fig. 6

Fig. 7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120
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(intron)
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181
240
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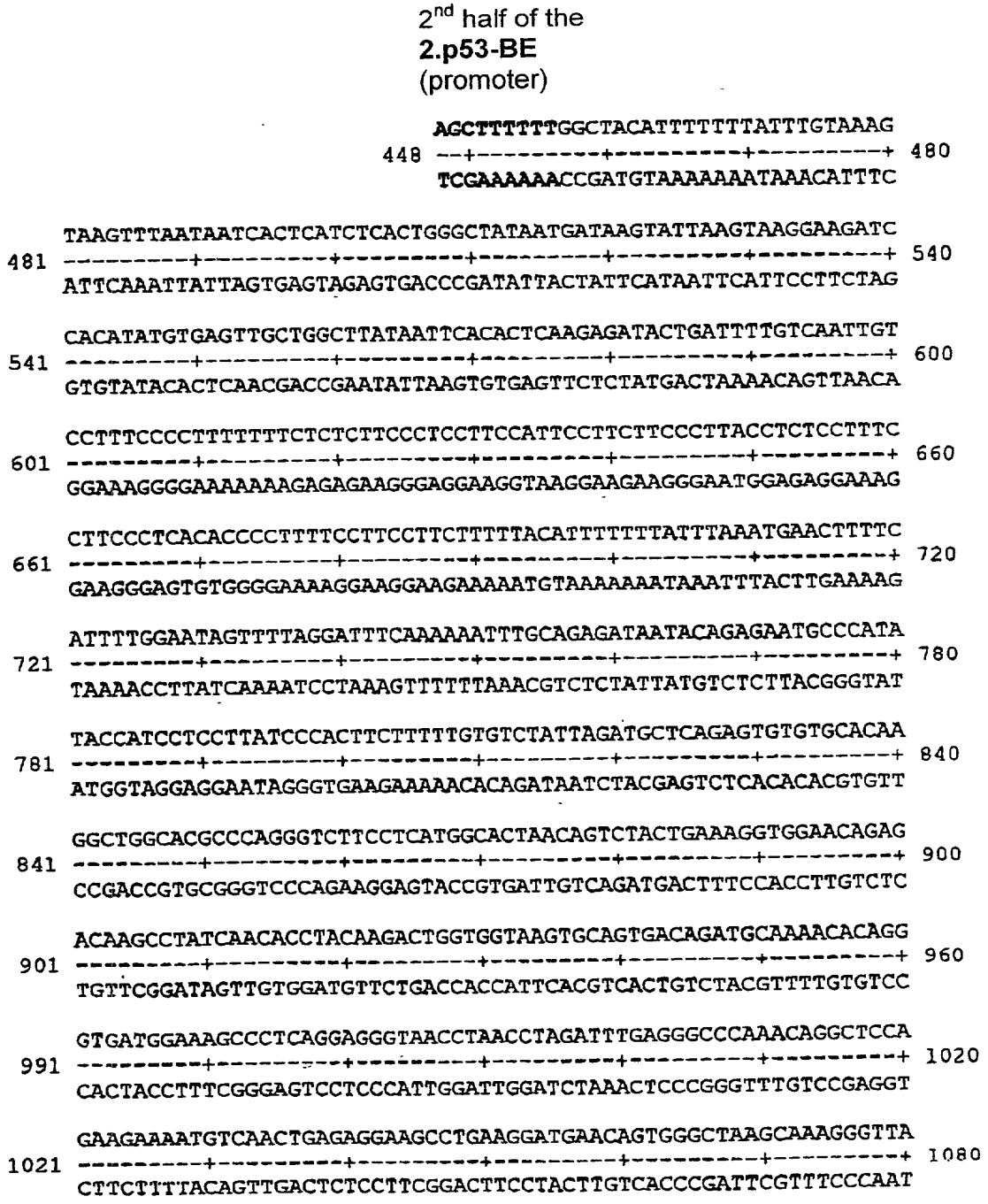
Fig. 8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(promoter)
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541
600
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CCTTTCCCCTTTTTTTCTCTCTTCCCTCCTTCCATTCCTTCTTCCCTTACCTCTCCTTTC
601
660
GGAAAGGGGAAAAAAAGAGAGAAGGGAGGAAGGTAAGGAAGAAGGGAATGGAGAGGAAAG
CTTCCCTCACACCCCTTTTCCTTCCTTCTTTTTACATTTTTTTATTTAAATGAACTTTTC
661
720
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ATTTTGGAATAGTTTTAGGATTTCAAAAAATTTGCAGAGATAATACAGAGAATGCCCATA
721
780
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TACCATCCTCCTTATCCCACTTCTTTTTGTGTCTATTAGATGCTCAGAGTGTGTGCACAA
781
840
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GGCTGGCACGCCCAGGGTCTTCCTCATGGCACTAACAGTCTACTGAAAGGTGGAACAGAG
841
900
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901
960
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991
1020
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GAAGAAAATGTCAACTGAGAGGAAGCCTGAAGGATGAACAGTGGGCTAAGCAAAGGGTTA
1021
1080
CTTCTTTTACAGTTGACTCTCCTTCGGACTTCCTACTTGTCACCCGATTCGTTTCCCAAT

Fig. 8 (cont'd I)

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     TTAATGTGTTATTAATGGGTTGAATCTAATTGGGAAGGGAGAGAGGTTGCAGAGTGAGGT
1081 ---------+---------+---------+---------+---------+---------+ 1140
     AATTACACAATAATTACCCAACTTAGATTAACCCTTCCCTCTCTCCAACGTCTCACTCCA

     GCAGAGCTTGGTGGACGATGCCAAAGGAATACTGAAACCTTTAGTGTGTCCAGTCTGGAA
1141 ---------+---------+---------+---------+---------+---------+ 1200
     CGTCTCGAACCACCTGCTACGGTTTCCTTATGACTTTGGAAATCACACAGGTCAGACCTT

     CTGCATCCAAATTCAGGTTCAGTAATGATGTCATTATCCAAACATACCTTCTGTAAAATT
1201 ---------+---------+---------+---------+---------+---------+ 1260
     GACGTAGGTTTAAGTCCAAGTCATTACTACAGTAATAGGTTTGTATGGAAGACATTTTAA
```

←--- 3.p53-BE ----→
(promoter)

```
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1261 ---------+---------+---------+---------+---------+---------+ 1320
     GTACGATTTGATGGATTCTCGATAGATGGCAAGGTTTCGTTATCACTGAAACTTGTCACA

     TCACCAGAGCACGAAAGAATTACAAGATTTTTTTTTAAAGAAAATTGGCCAGGAAATAAT
1321 ---------+---------+---------+---------+---------+---------+ 1380
     AGTGGTCTCGTGCTTTCTTAATGTTCTAAAAAAAAATTTCTTTTAACCGGTCCTTTATTA

     GAGTAACGAAGGACAGGAAGTAATTGTGAATGTTTAATATAGCTGGGGCTATGCGATTTG
1381 ---------+---------+---------+---------+---------+---------+ 1440
     CTCATTGCTTCCTGTCCTTCATTAACACTTACAAATTATATCGACCCCGATACGCTAAAC

     GCTTAAGTTGTTAGCTTTGTTTTCCTCTTGAGAAATAAAAACTAAGGGGCCCTCCCTTTT
1441 ---------+---------+---------+---------+---------+---------+ 1500
     CGAATTCAACAATCGAAACAAAAGGAGAACTCTTTATTTTTGATTCCCCGGGAGGGAAAA

     CAGAGCCCTATGGCGCAACATCTGTACTTTTTCATATGGTTAACTGTCCATTCCAGGAAC
1501 ---------+---------+---------+---------+---------+---------+ 1560
     GTCTCGGGATACCGCGTTGTAGACATGAAAAAGTATACCAATTGACAGGTAAGGTCCTTG

     GTCTGTGAGCCTCTCATGTTGCAGCCACAACATGGACAGCCCAGTCAAATGCCCCGCAAG
1561 ---------+---------+---------+---------+---------+---------+ 1620
     CAGACACTCGGAGAGTACAACGTCGGTGTTGTACCTGTCGGGTCAGTTTACGGGGCGTTC

     TCTTTCTCTGAGTGACTCCAGCAATTAGCCAAGGCTCCTGTACCCAGGCAGGACCTCTGC
1621 ---------+---------+---------+---------+---------+---------+ 1680
     AGAAAGAGACTCACTGAGGTCGTTAATCGGTTCCGAGGACATGGGTCCGTCCTGGAGACG

     GCTCTGAGCTCCATTCTCCTTCAAGACCTCCCCAACTTCCCAGGTTGAACTACAGCAGAA
1681 ---------+---------+---------+---------+---------+---------+ 1740
     CGAGACTCGAGGTAAGAGGAAGTTCTGGAGGGGTTGAAGGGTCCAACTTGATGTCGTCTT

     GCCTTTAGAAAGGGCAGGAGGCCGGCTCTCGAGGTCCTCACCTGAAGTGAGCATGCCAGC
1741 ---------+---------+---------+---------+---------+---------+ 1800
     CGGAAATCTTTCCCGTCCTCCGGCCGAGAGCTCCAGGAGTGGACTTCACTCGTACGGTCG

     CACTGCAGGAACGCCCCGGGACAGGAATGCCCATTTGTGCAACGAACCCTGACTCCTTCC
1801 ---------+---------+---------+---------+---------+---------+ 1860
     GTGACGTCCTTGCGGGGCCCTGTCCTTACGGGTAAACACGTTGCTTGGGACTGAGGAAGG

     TCACCCTGACTTCTCCCCCTCCCTACCCGCGCGCAGGCCAAGTTGCTGAATCAATGGAGC
1861 ---------+---------+---------+---------+---------+---------+ 1920
     AGTGGGACTGAAGAGGGGGAGGGATGGGCGCGCGTCCGGTTCAACGACTTAGTTACCTCG
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Patent Publication

Fig. 8 (cont'd II)

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     CCTCCCCAACCCGGGCGTTCCCCAGCGAGGCTTCCTTCCCATCCTCCTGACCACCGGGGC
1921 ---------+---------+---------+---------+---------+---------+ 1980
     GGAGGGGTTGGGCCCGCAAGGGGTCGCTCCGAAGGAAGGGTAGGAGGACTGGTGGCCCCG

     TTTTCGTGAGCTCGTCTCTGATCTCGCGCAAGAGTGACACACAGGTGTTCAAAGACGCTT
1981 ---------+---------+---------+---------+---------+---------+ 2040
     AAAAGCACTCGAGCAGAGACTAGAGCGCGTTCTCACTGTGTGTCCACAAGTTTCTGCGAA

     CTGGGGAGTGAGGGAAGCGGTTTACGAGTGACTTGGCTGGAGCCTCAGGGGCGGGCACTG
2041 ---------+---------+---------+---------+---------+---------+ 2100
     GACCCCTCACTCCCTTCGCCAAATGCTCACTGAACCGACCTCGGAGTCCCCGCCCGTGAC

     GCACGGAACACACCCTGAGGCCAGCCCTGGCTGCCCAGGCGGAGCTGCCTCTTCTCCCGC
2101 ---------+---------+---------+---------+---------+---------+ 2160
     CGTGCCTTGTGTGGGACTCCGGTCGGGACCGACGGGTCCGCCTCGACGGAGAAGAGGGCG

     GGACATGTACAGAGCTCGAGAAGTACTAGTGGCCACGTGGGCCGTGCACCTTAAGCTTTA
2161 ---------+---------+---------+---------+---------+---------+ 2220
     CCTGTACATGTCTCGAGCTCTTCATGATCACCGGTGCACCCGGCACGTGGAATTCGAAAT
```

←---4.p53-BE-
(intron)

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     GGGTCGCTGGAGGGGGACCCCGGTTGGAGAGAGGAGCGGAACTCCTGGACAAGCCCTGAC
2221 ---------+---------+---------+---------+---------+---------+ 2280
     CCCAGCGACCTCCCCCTGGGGCCAACCTCTCTCCTCGCCTTGAGGACCTGTTCGGGACTG

     ----→

     AAGCCAAGCCAAAGGTCCGCTCCGGCGCGGGTGGGTGAGTGCGCGCCGCCCCGCGGGGGC
2281 ---------+---------+---------+---------+---------+---------+ 2340
     TTCGGTTCGGTTTCCAGGCGAGGCCGCGCCCACCCACTCACGCGCGGCGGGGCGCCCCCG

     GGGGAGAGAGCCTGCAGCCTTCAGAACAGATATTGCTCATTTTCTGGCAGTTCTCAGACG
2341 ---------+---------+---------+---------+---------+---------+ 2400
     CCCCTCTCTCGGACGTCGGAAGTCTTGTCTATAACGAGTAAAAGACCGTCAAGAGTCTGC

     TAGGAAATAAGTCAGCACCGAAGCAGTGGTTAAGCCGGAGGGCTCGGAAGAACGGCACCT
2401 ---------+---------+---------+---------+---------+---------+ 2460
     ATCCTTTATTCAGTCGTGGCTTCGTCACCAATTCGGCCTCCCGAGCCTTCTTGCCGTGGA

     TTTCTTTCTCGAAAAAGTTATATGGGGGCTGAATGAGCTTCTGGAGGCTTGTTTACCGTT
2461 ---------+---------+---------+---------+---------+---------+ 2520
     AAAGAAAGAGCTTTTTCAATATACCCCCGACTTACTCGAAGACCTCCGAACAAATGGCAA

     TTTTATTGTCACACAGAAAAGGAAACTGCCTTGTCTCCCTTCCGGGAATTCTCTCTTTAA
2521 ---------+---------+---------+---------+---------+---------+ 2580
     AAAATAACAGTGTGTCTTTTCCTTTGACGGAACAGAGGGAAGGCCCTTAAGAGAGAAATT

     GACTGTAAGTCGCTGCCTGAGTGGTTTCATTTTGTTTTGTTTTTCTGCCCTTCTCTTTCT
2581 ---------+---------+---------+---------+---------+---------+ 2640
     CTGACATTCAGCGACGGACTCACCAAAGTAAAACAAAACAAAAAGACGGGAAGAGAAAGA

     TCTTTTGCCCTTTCTTAGCTTGCACTCCCATGGTGATTTCTGCTTGGTCTCCTGCTGGGG
2641 ---------+---------+---------+---------+---------+---------+ 2700
     AGAAAACGGGAAAGAATCGAACGTGAGGGTACCACTAAAGACGAACCAGAGGACGACCCC
```

Document #: 1 Page: 10 of 26

Fig. 8 (cont'd III)

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2701 ---------+---------+---------+---------+---------+---------+ 2760
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    GCAGCCTGTTTTGAAAAGTCCCTCGCTCAGAAATGCCAGCTTGCAGATGGCTAATCAAAG
2761 ---------+---------+---------+---------+---------+---------+ 2820
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2821 ------- 2827
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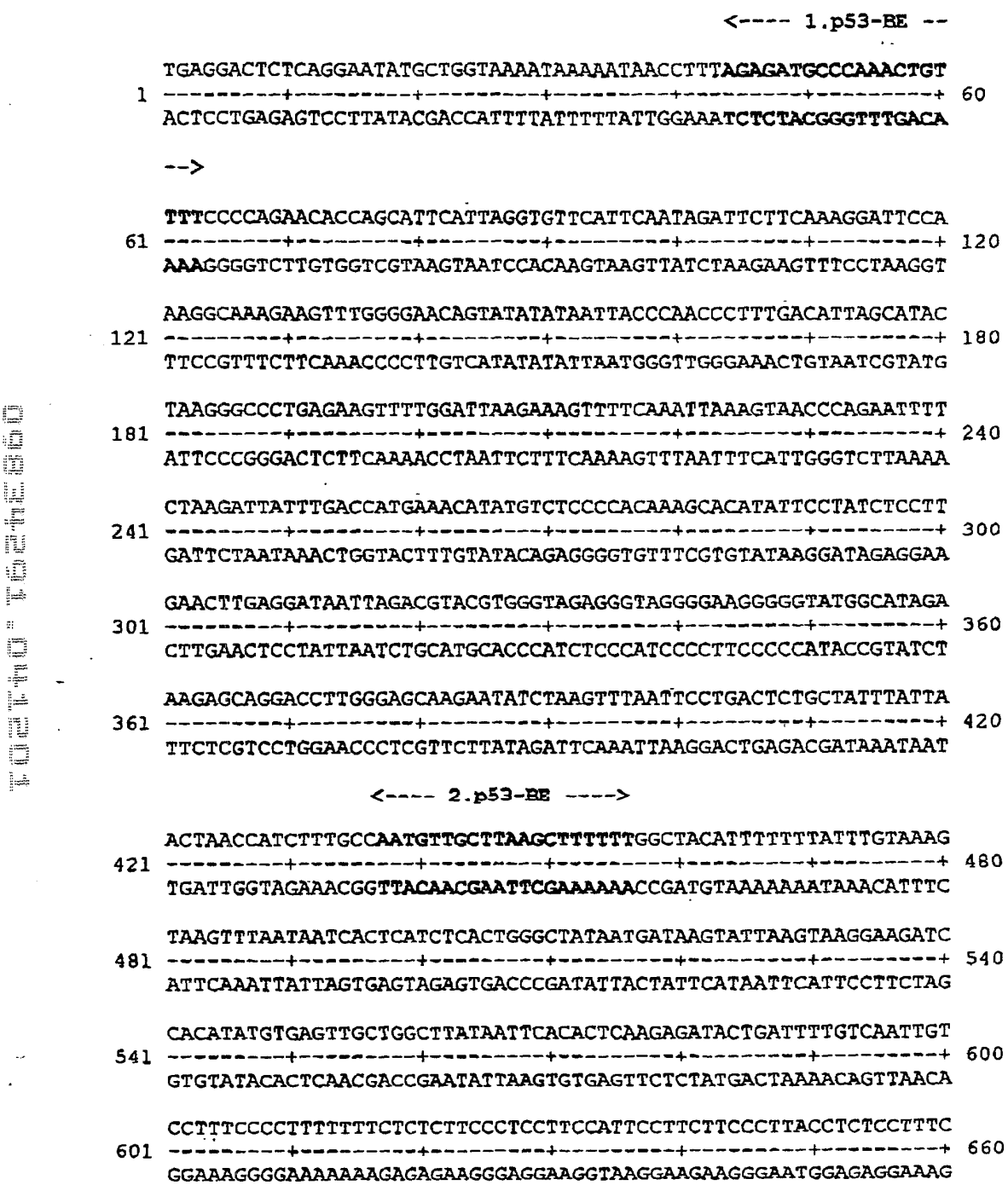
Substitute Sheet (Rule 26)

Fig. 9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1
61
121
181
241
301
361
421
481
541
601
60
120
180
240
300
360
420
480
540
600
660

Fig. 9 (cont'd I)

```
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661 ---------+---------+---------+---------+---------+---------+ 720
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    ATTTTGGAATAGTTTTAGGATTTCAAAAAATTTGCAGAGATAATACAGAGAATGCCCATA
721 ---------+---------+---------+---------+---------+---------+ 780
    TAAAACCTTATCAAAATCCTAAAGTTTTTTAAACGTCTCTATTATGTCTCTTACGGGTAT

    TACCATCCTCCTTATCCCACTTCTTTTTGTGTCTATTAGATGCTCAGAGTGTGTGCACAA
781 ---------+---------+---------+---------+---------+---------+ 840
    ATGGTAGGAGGAATAGGGTGAAGAAAAACACAGATAATCTACGAGTCTCACACACGTGTT

    GGCTGGCACGCCCAGGGTCTTCCTCATGGCACTAACAGTCTACTGAAAGGTGGAACAGAG
841 ---------+---------+---------+---------+---------+---------+ 900
    CCGACCGTGCGGGTCCCAGAAGGAGTACCGTGATTGTCAGATGACTTTCCACCTTGTCTC

    ACAAGCCTATCAACACCTACAAGACTGGTGGTAAGTGCAGTGACAGATGCAAAACACAGG
901 ---------+---------+---------+---------+---------+---------+ 960
    TGTTCGGATAGTTGTGGATGTTCTGACCACCATTCACGTCACTGTCTACGTTTTGTGTCC

    GTGATGGAAAGCCCTCAGGAGGGTAACCTAACCTAGATTTGAGGGCCCAAACAGGCTCCA
991 ---------+---------+---------+---------+---------+---------+ 1020
    CACTACCTTTCGGGAGTCCTCCCATTGGATTGGATCTAAACTCCCGGGTTTGTCCGAGGT

    GAAGAAAATGTCAACTGAGAGGAAGCCTGAAGGATGAACAGTGGGCTAAGCAAAGGGTTA
1021 ---------+---------+---------+---------+---------+---------+ 1080
    CTTCTTTTACAGTTGACTCTCCTTCGGACTTCCTACTTGTCACCCGATTCGTTTCCCAAT

    TTAATGTGTTATTAATGGGTTGAATCTAATTGGGAAGGGAGAGAGGTTGCAGAGTGAGGT
1081 ---------+---------+---------+---------+---------+---------+ 1140
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    GCAGAGCTTGGTGGACGATGCCAAAGGAATACTGAAACCTTTAGTGTGTCCAGTCTGGAA
1141 ---------+---------+---------+---------+---------+---------+ 1200
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    CTGCATCCAAATTCAGGTTCAGTAATGATGTCATTATCCAAACATACCTTCTGTAAAATT
1201 ---------+---------+---------+---------+---------+---------+ 1260
    GACGTAGGTTTAAGTCCAAGTCATTACTACAGTAATAGGTTTGTATGGAAGACATTTTAA

         <---- 3.p53-BE ---->

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1261 ---------+---------+---------+---------+---------+---------+ 1320
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    TCACCAGAGCACGAAAGAATTACAAGATTTTTTTTTAAAGAAAATTGGCCAGGAAATAAT
1321 ---------+---------+---------+---------+---------+---------+ 1380
    AGTGGTCTCGTGCTTTCTTAATGTTCTAAAAAAAAATTTCTTTTAACCGGTCCTTTATTA

    GAGTAACGAAGGACAGGAAGTAATTGTGAATGTTTAATATAGCTGGGGCTATGCGATTTG
1381 ---------+---------+---------+---------+---------+---------+ 1440
    CTCATTGCTTCCTGTCCTTCATTAACACTTACAAATTATATCGACCCCGATACGCTAAAC

    GCTTAAGTTGTTAGCTTTGTTTTCCTCTTGAGAAATAAAAACTAAGGGGCCCTCCCTTTT
1441 ---------+---------+---------+---------+---------+---------+ 1500
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    CAGAGCCCTATGGCGCAACATCTGTACTTTTTCATATGGTTAACTGTCCATTCCAGGAAC
1501 ---------+---------+---------+---------+---------+---------+ 1560
    GTCTCGGGATACCGCGTTGTAGACATGAAAAAGTATACCAATTGACAGGTAAGGTCCTTG
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Document: Dec 14, 2001

Fig. 9 (cont'd II)

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    TCTTTCTCTGAGTGACTCCAGCAATTAGCCAAGGCTCCTGTACCCAGGCAGGACCTCTGC
1621 ---------+---------+---------+---------+---------+---------+ 1680
    AGAAAGAGACTCACTGAGGTCGTTAATCGGTTCCGAGGACATGGGTCCGTCCTGGAGACG

    GCTCTGAGCTCCATTCTCCTTCAAGACCTCCCCAACTTCCCAGGTTGAACTACAGCAGAA
1681 ---------+---------+---------+---------+---------+---------+ 1740
    CGAGACTCGAGGTAAGAGGAAGTTCTGGAGGGGTTGAAGGGTCCAACTTGATGTCGTCTT

    GCCTTTAGAAAGGGCAGGAGGCCGGCTCTCGAGGTCCTCACCTGAAGTGAGCATGCCAGC
1741 ---------+---------+---------+---------+---------+---------+ 1800
    CGGAAATCTTTCCCGTCCTCCGGCCGAGAGCTCCAGGAGTGGACTTCACTCGTACGGTCG

    CACTGCAGGAACGCCCCGGGACAGGAATGCCCATTTGTGCAACGAACCCTGACTCCTTCC
1801 ---------+---------+---------+---------+---------+---------+ 1860
    GTGACGTCCTTGCGGGGCCCTGTCCTTACGGGTAAACACGTTGCTTGGGACTGAGGAAGG

    TCACCCTGACTTCTCCCCCTCCCTACCCGCGCGCAGGCCAAGTTGCTGAATCAATGGAGC
1861 ---------+---------+---------+---------+---------+---------+ 1920
    AGTGGGACTGAAGAGGGGGAGGGATGGGCGCGCGTCCGGTTCAACGACTTAGTTACCTCG

    CCTCCCCAACCCGGGCGTTCCCCAGCGAGGCTTCCTTCCCATCCTCCTGACCACCGGGGC
1921 ---------+---------+---------+---------+---------+---------+ 1980
    GGAGGGGTTGGGCCCGCAAGGGGTCGCTCCGAAGGAAGGGTAGGAGGACTGGTGGCCCCG

    TTTTCGTGAGCTCGTCTCTGATCTCGCGCAAGAGTGACACACAGGTGTTCAAAGACGCTT
1981 ---------+---------+---------+---------+---------+---------+ 2040
    AAAAGCACTCGAGCAGAGACTAGAGCGCGTTCTCACTGTGTGTCCACAAGTTTCTGCGAA

    CTGGGGAGTGAGGGAAGCGGTTTACGAGTGACTTGGCTGGAGCCTCAGGGGCGGGCACTG
2041 ---------+---------+---------+---------+---------+---------+ 2100
    GACCCCTCACTCCCTTCGCCAAATGCTCACTGAACCGACCTCGGAGTCCCCGCCCGTGAC

    GCACGGAACACACCCTGAGGCCAGCCCTGGCTGCCCAGGCGGAGCTGCCTCTTCTCCCGC
2101 ---------+---------+---------+---------+---------+---------+ 2160
    CGTGCCTTGTGTGGGACTCCGGTCGGGACCGACGGGTCCGCCTCGACGGAGAAGAGGGCG

    GGACATGTACAGAGCTCGAGAAGTACTAGTGGCCACGTGGGCCGTGCACCTTAAGCTTTA
2161 ---------+---------+---------+---------+---------+---------+ 2220
    CCTGTACATGTCTCGAGCTCTTCATGATCACCGGTGCACCCGGCACGTGGAATTCGAAAT

                                                  <---- 4.p53-BE
                                                  (intron)

    GGGTCGCTGGAGGGGGACCCCGGTTGGAGAGAGGAGCGGAACTCCTGGACAAGCCCTGAC
2221 ---------+---------+---------+---------+---------+---------+ 2280
    CCCAGCGACCTCCCCCTGGGGCCAACCTCTCTCCTCGCCTTGAGGACCTGTTCGGGACTG

    ----->

    AAGCCAAGCCAAAGGTCCGCTCCGGCGCGGGTGGGTGAGTGCGCGCCGCCCCGCGGGGGC
2281 ---------+---------+---------+---------+---------+---------+ 2340
    TTCGGTTCGGTTTCCAGGCGAGGCCGCGCCCACCCACTCACGCGCGGCGGGGCGCCCCCG

    GGGGAGAGAGCCTGCAGCCTTCAGAACAGATATTGCTCATTTTCTGGCAGTTCTCAGACG
2341 ---------+---------+---------+---------+---------+---------+ 2400
    CCCCTCTCTCGGACGTCGGAAGTCTTGTCTATAACGAGTAAAAGACCGTCAAGAGTCTGC
```
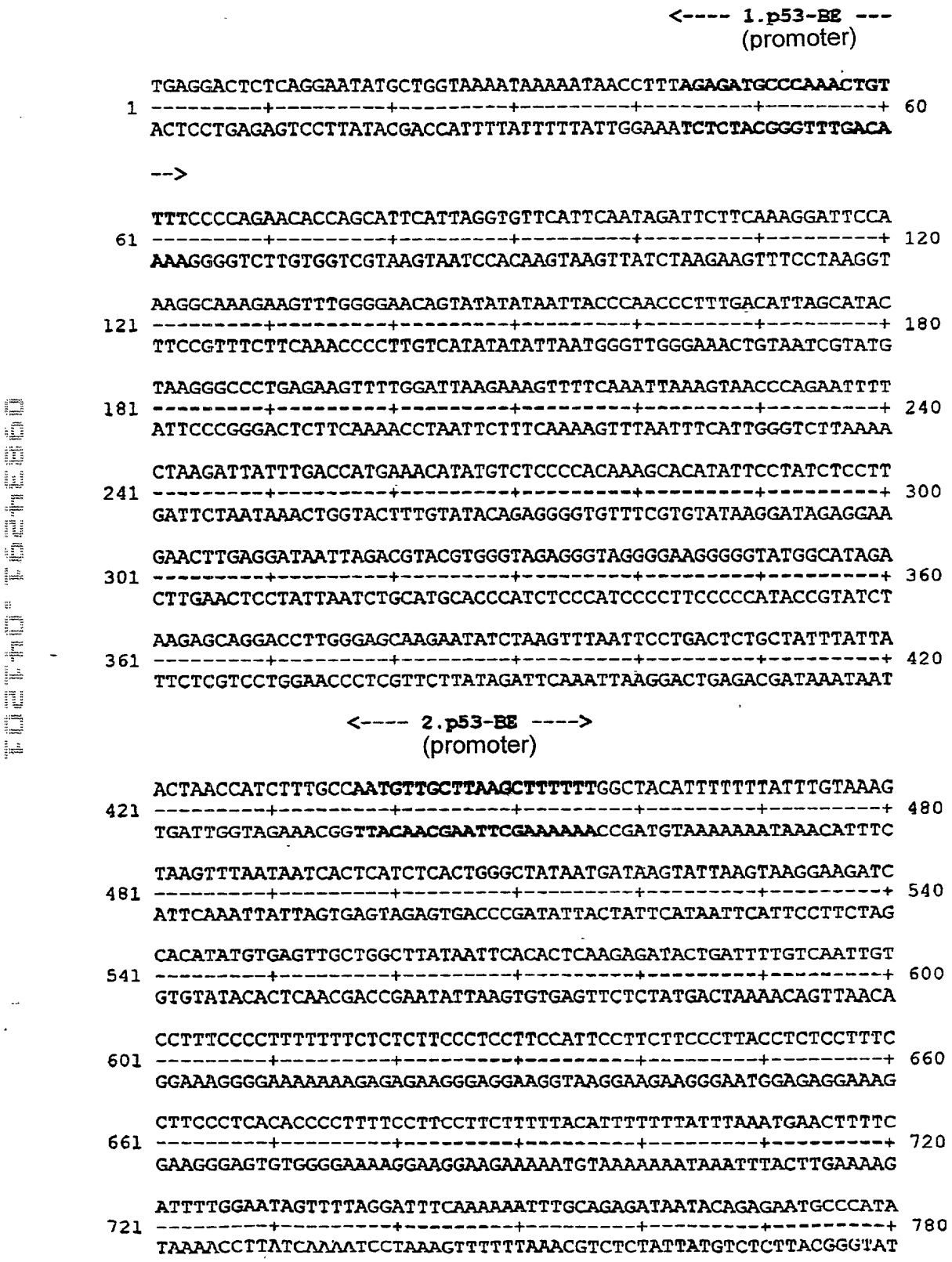

SUBSTITUTE SHEET (RULE 26)

Fig. 9 (cont'd III)

```
     TAGGAAATAAGTCAGCACCGAAGCAGTGGTTAAGCCGGAGGGCTCGGAAGAACGGCACCT
2401 ---------+---------+---------+---------+---------+---------+ 2460
     ATCCTTTATTCAGTCGTGGCTTCGTCACCAATTCGGCCTCCCGAGCCTTCTTGCCGTGGA

     TTTCTTTCTCGAAAAAGTTATATGGGGGCTGAATGAGCTTCTGGAGGCTTGTTTACCGTT
2461 ---------+---------+---------+---------+---------+---------+ 2520
     AAAGAAAGAGCTTTTTCAATATACCCCCGACTTACTCGAAGACCTCCGAACAAATGGCAA

     TTTTATTGTCACACAGAAAAGGAAACTGCCTTGTCTCCCTTCCGGGAATTCTCTCTTTAA
2521 ---------+---------+---------+---------+---------+---------+ 2580
     AAAATAACAGTGTGTCTTTTCCTTTGACGGAACAGAGGGAAGGCCCTTAAGAGAGAAATT

     GACTGTAAGTCGCTGCCTGAGTGGTTTCATTTTGTTTTGTTTTTCTGCCCTTCTCTTTCT
2581 ---------+---------+---------+---------+---------+---------+ 2640
     CTGACATTCAGCGACGGACTCACCAAAGTAAAACAAAACAAAAAGACGGGAAGAGAAAGA

     TCTTTTGCCCTTTCTTAGCTTGCACTCCCATGGTGATTTCTGCTTGGTCTCCTGCTGGGG
2641 ---------+---------+---------+---------+---------+---------+ 2700
     AGAAAACGGGAAAGAATCGAACGTGAGGGTACCACTAAAGACGAACCAGAGGACGACCCC

     TTGGTGGTACTCGTTCCCACCGCACAGAACCCGGCGCCTATTATTGGCCAAGAAACTTGA
2701 ---------+---------+---------+---------+---------+---------+ 2760
     AACCACCATGAGCAAGGGTGGCGTGTCTTGGGCCGCGGATAATAACCGGTTCTTTGAACT

     GCAGCCTGTTTTGAAAAGTCCCTCGCTCAGAAATGCCAGCTTGCAGATGGCTAATCAAAG
2761 ---------+---------+---------+---------+---------+---------+ 2820
     CGTCGGACAAAACTTTTCAGGGAGCGAGTCTTTACGGTCGAACGTCTACCGATTAGTTTC

     AGACGTG
2821 ------- 2827
     TCTGCAC
```

SUBSTITUTE SHEET (RULE 26)

Fig. 10



Replacement Sheet

Fig. 10 (cont'd I)

```
     TACCATCCTCCTTATCCCACTTCTTTTTGTGTCTATTAGATGCTCAGAGTGTGTGCACAA
781  ---------+---------+---------+---------+---------+---------+ 840
     ATGGTAGGAGGAATAGGGTGAAGAAAAACACAGATAATCTACGAGTCTCACACACGTGTT

     GGCTGGCACGCCCAGGGTCTTCCTCATGGCACTAACAGTCTACTGAAAGGTGGAACAGAG
841  ---------+---------+---------+---------+---------+---------+ 900
     CCGACCGTGCGGGTCCCAGAAGGAGTACCGTGATTGTCAGATGACTTTCCACCTTGTCTC

     ACAAGCCTATCAACACCTACAAGACTGGTGGTAAGTGCAGTGACAGATGCAAAACACAGG
901  ---------+---------+---------+---------+---------+---------+ 960
     TGTTCGGATAGTTGTGGATGTTCTGACCACCATTCACGTCACTGTCTACGTTTTGTGTCC

     GTGATGGAAAGCCCTCAGGAGGGTAACCTAACCTAGATTTGAGGGCCCAACAGGCTCCAG
961  ---------+---------+---------+---------+---------+---------+ 1020
     CACTACCTTTCGGGAGTCCTCCCATTGGATTGGATCTAAACTCCCGGGTTGTCCGAGGTC

     AAGAAAATGTCAACTGAGAGGAAGCCTGAAGGATGAACAGTGGGCTAAGCAAAGGGTTAT
1021 ---------+---------+---------+---------+---------+---------+ 1080
     TTCTTTTACAGTTGACTCTCCTTCGGACTTCCTACTTGTCACCCGATTCGTTTCCCAATA

     TAATGTGTTATTAATGGGTTGAATCTAATTGGGAAGGGAGAGAGGTTGCAGAGTGAGGTG
1081 ---------+---------+---------+---------+---------+---------+ 1140
     ATTACACAATAATTACCCAACTTAGATTAACCCTTCCCTCTCTCCAACGTCTCACTCCAC

     CAGAGCTTGGTGGACGATGCCAAAGGAATACTGAAACCTTTAGTGTGTCCAGTCTGGAAC
1141 ---------+---------+---------+---------+---------+---------+ 1200
     GTCTCGAACCACCTGCTACGGTTTCCTTATGACTTTGGAAATCACACAGGTCAGACCTTG

     TGCATCCAAATTCAGGTTCAGTAATGATGTCATTATCCAAACATACCTTCTGTAAAATTC
1201 ---------+---------+---------+---------+---------+---------+ 1260
     ACGTAGGTTTAAGTCCAAGTCATTACTACAGTAATAGGTTTGTATGGAAGACATTTTAAG

          <---- 3.p53-BE ---->
               (promoter)

     ATGCTAAACTACCTAAGAGCTATCTACCGTTCCAAAGCAATAGTGACTTTGAACAGTGTT
1261 ---------+---------+---------+---------+---------+---------+ 1320
     TACGATTTGATGGATTCTCGATAGATGGCAAGGTTTCGTTATCACTGAAACTTGTCACAA

     CACCAGAGCACGAAAGAATTACAAGATTTTTTTTTAAAGAAAATTGGCCAGGAAATAATG
1321 ---------+---------+---------+---------+---------+---------+ 1380
     GTGGTCTCGTGCTTTCTTAATGTTCTAAAAAAAAATTTCTTTTAACCGGTCCTTTATTAC

     AGTAACGAAGGACAGGAAGTAATTGTGAATGTTTAATATAGCTGGGGCTATGCGATTTGG
1381 ---------+---------+---------+---------+---------+---------+ 1440
     TCATTGCTTCCTGTCCTTCATTAACACTTACAAATTATATCGACCCCGATACGCTAAACC

     CTTAAGTTGTTAGCTTTGTTTTCCTCTTGAGAAATAAAAACTAAGGGGCCCTCCCTTTTC
1441 ---------+---------+---------+---------+---------+---------+ 1500
     GAATTCAACAATCGAAACAAAAGGAGAACTCTTTATTTTTGATTCCCCGGGAGGGAAAAG

     AGAGCCTTATGGCGCAACATCTGTACTTTTTCATATGGTTAACTGTCCATTCCAGAAACG
1501 ---------+---------+---------+---------+---------+---------+ 1560
     TCTCGGAATACCGCGTTGTAGACATGAAAAAGTATACCAATTGACAGGTAAGGTCTTTGC

     TCTGTGAGCCTCTCATGTTGCAGCCACAACATGGACAGCCCAGTCAAATGCCCCGCAAGT
1561 ---------+---------+---------+---------+---------+---------+ 1620
     AGACACTCGGAGAGTACAACGTCGGTGTTGTACCTGTCGGGTCAGTTTACGGGGCGTTCA

     CTTTCTCTGAGTGACTCCAGCAATTAGCCAAGGCTCCTGTACCCAGGCAGGACCTCTGCG
1621 ---------+---------+---------+---------+---------+---------+ 1680
     GAAAGAGACTCACTGAGGTCGTTAATCGGTTCCGAGGACATGGGTCCGTCCTGGAGACGC

     CTCTGAGCTCCATTCTCCTTCAAGACCTCCCCAACTTCCCAGGTTGAACTACAGCAGAAG
1681 ---------+---------+---------+---------+---------+---------+ 1740
     GAGACTCGAGGTAAGAGGAAGTTCTGGAGGGGTTGAAGGGTCCAACTTGATGTCGTCTTC
```

Fig. 10 (cont'd II)

```
                CCTTTAGAAAGGGCAGGAGGCCGGCTCTCGAGGTCCTCACCTGAAGTGAGCATGCCAGCC
1741 ---------+---------+---------+---------+---------+---------+ 1800
                GGAAATCTTTCCCGTCCTCCGGCCGAGAGCTCCAGGAGTGGACTTCACTCGTACGGTCGG

                ACTGCAGGAACGCCCCGGGACAGGAATGCCCATTTGTGCAACGAACCCTGACTCCTTCCT
1801 ---------+---------+---------+---------+---------+---------+ 1860
                TGACGTCCTTGCGGGGCCCTGTCCTTACGGGTAAACACGTTGCTTGGGACTGAGGAAGGA

                CACCCTGACTTCTCCCCCTCCCTACCCGCGCGCAGGCCAAGTTGCTGAATCAATGGAGCC
1861 ---------+---------+---------+---------+---------+---------+ 1920
                GTGGGACTGAAGAGGGGGAGGGATGGGCGCGCGTCCGGTTCAACGACTTAGTTACCTCGG

                CTCCCCAACCCGGGCGTTCCCCAGCGAGGCTTCCTTCCCATCCTCCTGACCACCGGGGCT
1921 ---------+---------+---------+---------+---------+---------+ 1980
                GAGGGGTTGGGCCCGCAAGGGGTCGCTCCGAAGGAAGGGTAGGAGGACTGGTGGCCCCGA

                TTTCGTGAGCTCGTCTCTGATCTCGCGCAAGAGTGACACACAGGTGTTCAAAGACGCTTC
1981 ---------+---------+---------+---------+---------+---------+ 2040
                AAAGCACTCGAGCAGAGACTAGAGCGCGTTCTCACTGTGTGTCCACAAGTTTCTGCGAAG

                TGGGGAGTGAGGGAAGCGGTTTACGAGTGACTTGGCTGGAGCCTCAGGGGCGGGCACTGG
2041 ---------+---------+---------+---------+---------+---------+ 2100
                ACCCCTCACTCCCTTCGCCAAATGCTCACTGAACCGACCTCGGAGTCCCCGCCCGTGACC

                CACGGAACACACCCTGAGGCCAGCCCTGGCTGCCCAGGCGGAGCTGCCTCTTCTCCCGCG
2101 ---------+---------+---------+---------+---------+---------+ 2160
                GTGCCTTGTGTGGGACTCCGGTCGGGACCGACGGGTCCGCCTCGACGGAGAAGAGGGCGC

                GGTTGGTGGACCCGCTCAGTACGGAGTTGGGGAAGCTCTTTCACTTCGGAGGATTGCTCA
2161 ---------+---------+---------+---------+---------+---------+ 2220
                CCAACCACCTGGGCGAGTCATGCCTCAACCCCTTCGAGAAAGTGAAGCCTCCTAACGAGT

                ACAACCATGCTGGGCATCTGGACCCTCCTACCTCTGGTGATCCCTCTCCTGCCCGGGTGG
2221 ---------+---------+---------+---------+---------+---------+ 2280
                TGTTGGTACGACCCGTAGACCTGGGAGGATGGAGACCACTAGGGAGAGGACGGGCCCACC

                AGGCTTACCCCGTCTTAGTCCCGGGGATAGGCAAAGTGGGGCGGGCGCGGGACGCGTGCG
2281 ---------+---------+---------+---------+---------+---------+ 2340
                TCCGAATGGGGCAGAATCAGGGCCCCTATCCGTTTCACCCCGCCCGCGCCCTGCGCACGC

                GGATTGCGGCGGCAGCGGCGCACGCGGGCACCTGGGAGCGGCGGGCTGCTGCGGGAGGCG
2341 ---------+---------+---------+---------+---------+---------+ 2400
                CCTAACGCCGCCGTCGCCGCGTGCGCCCGTGGACCCTCGCCGCCCGACGACGCCCTCCGC

                TTGGAGACTGGCTCCCGGGGGCTGTTAGGACCTTCCCTCAGGCCCGGGTGCTCAGAACGA
2401 ---------+---------+---------+---------+---------+---------+ 2460
                AACCTCTGACCGAGGGCCCCCGACAATCCTGGAAGGGAGTCCGGGCCCACGAGTCTTGCT

                TGGAGGACTTGCTTTTCTTGGGCCTTGATGCGAAGTGCTGATCCCGCTGGGCAGGCGGGG
2461 ---------+---------+---------+---------+---------+---------+ 2520
                ACCTCCTGAACGAAAAGAACCCGGAACTACGCTTCACGACTAGGGCGACCCGTCCGCCCC

                CAGCTCCGGCGCTCCTCGGAGACCACTGCGCTCCACGTTGAGGTGGGCGTGGGGGGCGGA
2521 ---------+---------+---------+---------+---------+---------+ 2580
                GTCGAGGCCGCGAGGAGCCTCTGGTGACGCGAGGTGCAACTCCACCCGCACCCCCCGCCT

                CAGGAATTGAAGCGGAAGTCTGGGAAGCTTTAGGGTCGCTGGAGGGGGACCCCGGTTGGA
2581 ---------+---------+---------+---------+---------+---------+ 2640
                GTCCTTAACTTCGCCTTCAGACCCTTCGAAATCCCAGCGACCTCCCCCTGGGGCCAACCT

                <---- 4.p53-BE ---->
                (intron)

                GAGAGGAGCGGAACTCCTGGACAAGCCCTGACAAGCCAAGCCAAAGGTCCGCTCCGGCGC
2641 ---------+---------+---------+---------+---------+---------+ 2700
                CTCTCCTCGCCTTGAGGACCTGTTCGGGACTGTTCGGTTCGGTTTCCAGGCGAGGCCGCG
```

Fig. 10 (cont'd III)

```
     GGGTGGGTGAGTGCGCGCCGCCCCGCGGGGGCGGGGAGAGAGCCTACAGCCTTCAGAACA
2701 ---------+---------+---------+---------+---------+---------+ 2760
     CCCACCCACTCACGCGCGGCGGGGCGCCCCCGCCCCTCTCTCGGATGTCGGAAGTCTTGT

     CATATTGCTCATTTTCTGGCAGTTCTCAGACGTAGGAAATAAGTCAGCACCGAAGCAGTG
2761 ---------+---------+---------+---------+---------+---------+ 2820
     GTATAACGAGTAAAAGACCGTCAAGAGTCTGCATCCTTTATTCAGTCGTGGCTTCGTCAC

     GTTAAGCCGGAGGGCTCGGAAGAACGGCACCTTTTCTTTCTCGAAAAAGTTATATGGGGG
2821 ---------+---------+---------+---------+---------+---------+ 2880
     CAATTCGGCCTCCCGAGCCTTCTTGCCGTGGAAAAGAAAGAGCTTTTTCAATATACCCCC

     CTGAATGAGCTTCTGGAGGCTTGTTTACCGTTTTTTATTGTCACACAGAAAAGGAAACTG
2881 ---------+---------+---------+---------+---------+---------+ 2940
     GACTTACTCGAAGACCTCCGAACAAATGGCAAAAAATAACAGTGTGTCTTTTCCTTTGAC

     CCTTGTCTCCCTTCCGGGAATTCTCTCTTTAAGACTGTAAGTCGCTGCCTGAGTGGTTTC
2941 ---------+---------+---------+---------+---------+---------+ 3000
     GGAACAGAGGGAAGGCCCTTAAGAGAGAAATTCTGACATTCAGCGACGGACTCACCAAAG

     ATTTTGTTTTGTTTTTCTGCCCTTCTCTTTCTTCTTTTGCCCTTTCTTAGCTTGCACTCC
3001 ---------+---------+---------+---------+---------+---------+ 3060
     TAAAACAAAACAAAAAGACGGGAAGAGAAAGAAGAAAACGGGAAAGAATCGAACGTGAGG

     CATGGTGATTTCTGCTTGGTCTCCTGCTGGGGTTGGTGGTACTCGTTCCCACCGCACAGA
3061 ---------+---------+---------+---------+---------+---------+ 3120
     GTACCACTAAAGACGAACCAGAGGACGACCCCAACCACCATGAGCAAGGGTGGCGTGTCT

     ACCCGGCGCCTATTATTGGCCAAGAAACTTGAGCAGCCTGTTTTGAAAAGTCCCTCGCTC
3121 ---------+---------+---------+---------+---------+---------+ 3180
     TGGGCCGCGGATAATAACCGGTTCTTTGAACTCGTCGGACAAAACTTTTCAGGGAGCGAG

     AGAAATGCCAGCTTGCAGATGGCTAATCAAAG
3181 ---------+---------+---------+-- 3212
     TCTTTACGGTCGAACGTCTACCGATTAGTTTC
```

Replacement Sheet

Fig 11

variations in the p53 binding region of figure 8

1. **p1140 IMI**

p1140 GGACAAGCCCTGACAAGCCA

p1140 IMI GGA**A**AAGCCCTGACAAGCCA

positions of the mutations (boldface and arrow): 2270 (C→A)

2. **p1140 IMII**

p1140 GGACAAGCCCTGACAAGCCA

p1140 IMII GGA**A**AAGCCCTGA**A**AAGCCA

positions of the mutations (boldface and arrow): 2270 (C→A)
2280 (C→A)

3. **p1140 IMIII**

p1140 GGACAAGCCCTGACAAGCCA

p1140 IMIII GGA**AAAT**CCCTGA**AAAT**CCA

positions of the mutations (boldface and arrow): 2270 (C→A)
2273 (G→T)
2280 (C→A)
2283 (G→T)

4. **p1140 IMIV**

p1140	GGACAAGCCCTGACAAGCCA
p1140 IMIV	G**C**ACAAGCCCT**C**ACAAGCCA
	↑ ↑

positions of the mutations (boldface and arrow): 2268 (G→T)

2278 (C→A)

Substitute Sheet (Rule 26)

Fig. 12

variations in the p53 binding regions of figure 9

1. p1141 IMIII

```
p1141          GGACAAGCCCTGACAAGCCA
p1141 IMIII    GGAAAATCCCTGAAAATCCA
                 ↑  ↑      ↑  ↑
```

positions of the mutations (boldface and arrow): 2270
2273
2280
2283

2. p1141 1p53

```
p1141          AGAGATGCCCAAACTGTTTT
p1141 1p53     AGAGATTCCCAAAATGTTTT
                     ↑       ↑
```

positions of the mutations (boldface and arrow): 50
57

3. p1141 2p53

```
p1141          AATGTTGCTTAAGCTTTTTT
p1141 2p53     AATGTTTCTTAAGATTTTTT
                     ↑       ↑
```

positions of the mutations (boldface and arrow): 443
450

4. p1141 3p53

```
p1141          AAACTACCTAAGAGCTATCT
p1141 3p53     ACAATACCTAAGAGCTATCT
                 ↑ ↑
```

positions of the mutations (boldface and arrow): 1268 (A→C)
1270 (C→A)

5. p1141 ΔBgl

```
                        <---- 1.p53-BE ---->
p1141          AATAACCTTTAGAGATGCCCAAACTGTTTTCCCCAGAACA
p1141ΔBgl      AATAACCTTTA--------------GATCTCCCCAGAACA
```

6. p1141 ΔSpe

```
                        <---- 2.p53-BE ---->
p1141          CATCTTTGCCAATGTTGCTTAAGCTTTTTTGGCTACATTT
p1141ΔBgl      CATCTTTGCCA--------------CTAGTGGCTACATTT
```

7. p1141 ΔMph

```
                        <---- 3.p53-BE ---->
p1141          AATTCATGCTAAACTACCTAAGAGCTATCTACCGTTCCAA
p1141ΔBgl      AATTCATGCTATGCA--------------TACCGTTCCAA
```

Fig. 13

variations in the p53 binding region of figure 10

1. p1142 TAG

mutation of the positions: 2227 (A→T)
2228 (T→A)

2. p1142 IMIII

p1142 GGACAAGCCCTGACAAGCCA

p1142 IMIII GGA**A**A**A**T**T**CCCTGA**A**A**A**T**T**CCA
↑ ↑ ↑ ↑

positions of the mutations (boldface and arrow): 2662 (C→A)
2665 (G→T)
2672 (C→A)
2675 (G→T)

3. . p1142 ΔBgl

<---- 1.p53-BE ---->
p1142 AATAACCTTT**AGAGATGCCCAAACTGTTTT**CCCCAGAACA
p1142ΔBgl AATAACCTTT**A**----------**GATCT**CCCCAGAACA

4. p1142 ΔSpe

<---- 2.p53-BE ---->
p1142 CATCTTTGCC**AATGTTGCTTAAGCTTTTTT**GGCTACATTT
p1142ΔBgl CATCTTTGCC**A**----------**CTAGT**GGCTACATTT

5. p1142 ΔMph

<----- 3.p53-BE ----->

p1142	AATTCATGCT**AAACTACCTAAGAGCTATCT**ACCGTTCCAA
p1142ΔBgl	AATTCATGCT**ATGCA**----------**T**ACCGTTCCAA

Replacement Sheet

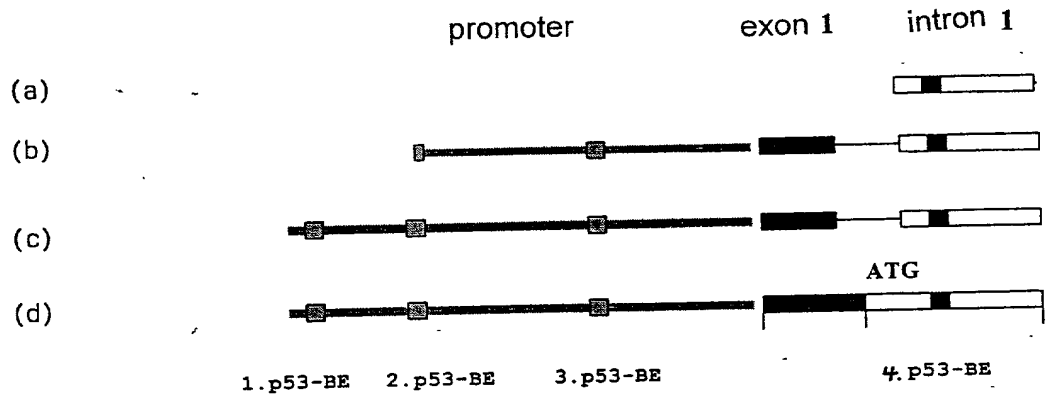

promoter
exon 1
intron 1
(a)
(b)
(c)
(d)
ATG
1.p53-BE
2.p53-BE
3.p53-BE
4.p53-BE

Fig. 14